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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,530	09/01/2006	Kaoru Miyamoto	1680/15	2171

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,530	MIYAMOTO ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8,10 and 11* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2, 7 and 9 have been canceled. Claim 11 has been added. Claims 1, 3-6, 8, 10 and 11 are pending.

Applicant's arguments filed 8-18-09 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claim 10 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12-16-08.

This application contains claim 10 drawn to an invention nonelected with traverse in the reply filed on 10-16-08. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1, 3-6, 8 and 11 are under consideration.

Claim Rejections - 35 USC § 112

Enablement

Claims 1, 3-6, 8 remain and claim 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for differentiating mesenchymal stem cells by transfecting the cells with a vector encoding steroidogenic factor 1 (sf-1) then stimulating the cells with cAMP such that the cells differentiate into

cells that produce progestin, androgen and androstendione, does not reasonably provide enablement for differentiating mesenchymal stem cells into any hormone-producing cells, using the sf-1 protein to induce differentiation in culture, inducing differentiation in the absence of cAMP or transplanting the cells in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to differentiating mesenchymal stem cells (MSC) into steroid hormone-producing cells by stimulating the cells by "a transcription factor, SF-1, in the presence of cAMP, wherein the hormones produced are selected from the group consisting of progestin, androgen, estrogen, glucocorticoid, and mineralcorticoid." The claim encompasses differentiating MSC into any cell that produces progestin, androgen, estrogen, glucocorticoid or mineralcorticoid. The claim also encompasses culturing MSC with sf-1 protein in the presence of cAMP to induce differentiation or transfecting MSC with DNA encoding sf-1 in the presence of cAMP to induce differentiation.

Val (Nuclear Receptor, 2003, Vol. 1, No. 8, pg 1-23) taught SF-1 acts on numerous genes, some of which are involved in hormone production (pg 7, "Genes implicated in steroidogenesis"). The effects of SF-1 on specific genes remain unclear (pg 9, col. 2 "SF-1 target genes: unanswered questions").

Crawford (Mol. Cell. Biol., July 1997, Vol. 17, No. 7, pg 3997-4006) taught differentiating embryonic stem (ES) cells by transfecting the cells with a vector encoding steroidogenic factor 1 (sf-1) then stimulating the cells with cAMP such that the cells

differentiate into cells that produce progesterone (pg 3998, col. 1, ES cell culture; pg 4000, col. 1, "ES cells differentiate…").

Example 1 (pg 6) shows the MSC transfected with a vector encoding SF-1 express p450scc but fail to show the cells produce pregnenolone or any other hormone claimed.

Example 2 (pg 7) shows MSC transfected with a vector encoding SF-1 cultured in the presence of cAMP express p450scc, HSD3b1, p450c17 and produce progesterone, androgen and androstenedione. Example 2 shows the cells express p450scc but fail to show the cells produce progestin, estrogen, glucocorticoid or mineralcorticoid as claimed.

Example 3 (pg 8) shows MSC transfected with a vector encoding SF-1 cultured in the presence of cAMP express StaR, P450scc and 3β-HSD, P450c21 and P45011b1. Example 3 fails to shows the cells produce any hormones as claimed.

Example 4 (pg 8) shows bone-marrow derived MSC (obtained from a Green rat apparently expressing GFP) transplanted into the testes of rats resulted in cells expressing GFP ("possibly derived from Green rat bone marrow" (pg 9, line 6) and P450scc. Example 4 fails to shows the cells expressing P450ssc WERE derived from the transplanted MSC or that the transplanted MSC produced hormones as claimed.

Example 5 (pg 9) shows differentiating MSC into cells that express p450scc, 3β-HSD, HSD3b1 and HSD3b6; however, the cells do not produce the hormones claimed.

The specification and the art at the time of filing do not teach the role of SF-1 in differentiating stem cells. The specification and the art at the time of filing do not teach

how to differentiate MSC transfected with a nucleic acid sequence encoding SF-1 into cells producing estrogen, glucocorticoid, and mineralcorticoid as specifically claimed. The specification and the art at the time of filing do not teach how to differentiate MSC into cells producing progestin, androgen, estrogen, glucocorticoid, and mineralcorticoid using SF-1 protein as broadly encompassed by the claim. The specification and the art at the time of filing are limited to differentiating MSC transfected with a nucleic acid sequence encoding SF-1 into cells producing progestin, androgen and androstendione. Given the unpredictability of the role of SF-1 in differentiation and the unpredictability of the effects of SF-1 on genes of interest taken with the limited teachings in the specification and the art at the time of filing, it would have required those of skill undue experimentation to determine how to differentiate MSC using SF-1 in the presence of cAMP into hormone-producing cells other than by transfecting the MSC with a nucleic acid sequence encoding SF-1, culturing the cells with cAMP and obtaining cells producing progestin, androgen and androstendione.

Claim 6 requires transplanting mesenchymal stem cells into a mammalian reproductive organ, wherein the mesenchymal stem cells contact extracellular components of the reproductive organ to induce SF-1 in the stem cells and thereby differentiate into steroid hormone-producing cells. The specification suggests transplanting the cells produced into a mammalian reproductive organ. The specification does not teach what type of cells are produced after differentiation, the amount of steroid produced by the cells, how to target the hormone produced to tissues of interest within the reproductive organ or how to differentiate cells in the absence of

cAMP as broadly encompassed by the claim. The art does not teach how to use non-descript cells that produce an undisclosed amount of hormone for transplantation into mammalian reproductive organs. Without such guidance, it would have required those of skill undue experimentation to determine how to use hormone-producing cells to mammalian reproductive organs.

Response to arguments

Applicants argue Val and Crawford do not discuss differentiating mesenchymal stem cells. Applicants' argument is not persuasive. Val indicates the unpredictable state of the art of the role of SF-1 in differentiation. Crawford indicates those of skill in the art at the time of filing were limited to using a vector encoding SF-1 to differentiate ES cells into hormone producing cells. Applicants' disclosure is similarly limited to using a vector encoding SF-1 to differentiate MSC. The specification and the art at the time of filing (including Val and Crawford) do not provide adequate guidance for those of skill to use SF-1 protein in culture to differentiate MSC (or any other stem cell) into a steroid producing cell as claimed.

Applicants point to Example 1 which teaches expressing p450scc in MSC transfected with SF-1. Applicants point out p450scc is associated with conversion of cholesterol to pregnenolone. Applicants' argument is not persuasive. Example 1 shows the cells express p450scc but fail to reasonably show the cells produce pregnenolone. Furthermore, pregnenolone is not in the list in claim 1 as amended.

Applicants point to Example 2 which teaches expressing p450scc, HSD3b1, p450c17 and producing progesterone, androgen and androstenedione in MSC

transfected with SF-1. Applicants' argument is not persuasive. Example 2 shows the cells express p450scc but fail to reasonably show the cells produce progestin, estrogen, glucocorticoid or mineralcorticoid as claimed.

Applicants point to Example 3 which does not teach making cells that produce any hormones.

Applicants point to Example 4 which teaches differentiating MSC into Leydig cells. Applicants' argument is not persuasive. While Leydig cell may produce testosterone, applicants fail to the differentiated cells DO produce testosterone.

Applicants point to Example 5 which teaches differentiating MSC into cells that express p450scc, 3β-HSD, HSD3b1 and HSD3b6. Applicants' argument is not persuasive because applicants do not show the cells produce the hormones claimed.

Pg 6 of applicants' arguments discusses differentiation in the absence of cAMP. IN particular, applicants argue Crawford does not relate to the state of the art at the time of filing because it is limited to ES cells. Applicants' argument is not persuasive because Crawford discusses the ability to differentiate pluripotent stem cells using a vector encoding steroidogenic factor 1 (sf-1); stimulating with cAMP is essential to differentiate the cells into cells that produce progesterone (pg 3998, col. 1, ES cell culture; pg 4000, col. 1, "ES cells differentiate…"). The specification does not provide adequate guidance to overcome this limitation in the art at the time of filing by teaching how to differentiate cells in the absence of cAMP as encompassed by claim 6.

Applicants argue Examples 2 and 4 differentiate cells in the absence of cAMP into cells that produce hormones as claimed. Applicants' argument is not persuasive.

Example 2, pg 7, lines 9 and 19, indicate the cells were cultured in the presence of cAMP. Example 4, pg 8-9, does not teach obtaining cells that produce hormones as claimed.

Indefiniteness

Claims 1-6, 8 and 9 remain and claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase “transcription factor, SF-1,...” in claim 1 does not make sense. As written, it appears the claim requires a transcription factor and SF-1 when in fact, applicants are attempting to state the transcription factor is SF-1. SF-1 stands for steroidogenic factor 1. The phrase” should be steroidogenic factor (SF-1).” Furthermore, SF-l in claim 1 should be SF-1. Replacing the phrase "transcription factor, SF-l" with "steroidogenic factor 1 (SF-1“) would overcome this rejection.

Claim 1 is also indefinite because “the hormones” lacks antecedent basis. The steroid producing cells may only produce one steroid. The phrase “wherein said hormone is selected…” would overcome this rejection.

Claim 6 does not make sense because it requires transplanting mesenchymal stem cells into a reproductive organ, but the cells contact extracellular components of the reproductive organ. It is wholly unclear how this can be or what applicants consider extracellular components of the reproductive organ. Furthermore, it is unclear how such “contact” induces SF-1 in the stem cells. If applicants intend the phrase “to induce SF-1 in the stem cells…” to be a functional limitation of the contacting step, the phrase should

be clearly set forth as "wherein said mesenchymal stem cells contact extracellular components of the reproductive organ such that SF-1 is expressed in the mesenchymal stem cells and differentiation of the mesenchymal stem cells into steroid hormone producing cells occurs."

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Gondo (Genes to Cells, 2004, Vol. 9, pg 1239-1247)

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Primary Patent Examiner